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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,324	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-9,11,15,22,41-47,50 and 51* is/are pending in the application.

4a) Of the above claim(s) *50 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-9,11,15,22 and 41-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 page / 02/23/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on April 8, 2010.

Status of Claims

Amendment of claims 1, 3 and 22 is acknowledged.

Claims 1, 3, 5-9, 11, 15, 22, 41-47 and 50-51 are currently pending and are the subject of this office action.

Claims 50 and 51 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention/species, there being no allowable generic or linking claim.

Claims 1, 3, 5-9, 11, 15, 22 and 41-47 are presently under examination.

The following species are currently under examination:

hydroxyurea as the second active agent, which was elected by Applicant in the reply filed on July 23, 2008.

Priority

The present application is a 371 of PCT/US03/11325 filed on 04/13/2003, and claims priority to provisional application No. 60/424,731 filed on 11/06/02.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated

(Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103 (Maintained rejection)

1) Claims 1, 5, 11, 15, 22 and new claims 41-47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, cited in previous office action) In view of Man et. al. (WO 2001/34606, cited in previous office action).

2) Claim 11 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, cited in previous office action) in view of Man et. al. (WO 2001/34606, cited in previous office action) as applied to claims 1, 5, 15, 22 and 41-47, further as evidenced by Canepa (British Journal of Haematology (2001) 115:313-315, cited in prior office action).

3) Claim 3 and 7-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, cited in prior office action) In view of Man et. al. (WO 2001/34606, cited in prior office action) as applied to claims 1, 5, 15, 22 and 41-47 above, and further in view of Alter et. al. (Blood (1985) 66:373-379, cited in prior office action).

4) Claim 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, cited in prior office action) In view of Man et. al. (WO 2001/34606, cited in prior office action) as applied to claims 1, 5, 15, 22 and 41-47 above, and further in view of Canepa et. al. (British Journal of Haematology (2001) 115:313-315, cited in prior office action).

The reasons for this rejection have been provided in the previous office action dated December 28, 2009, the text of which is incorporated by reference herein.

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues:

The rejection is based the allegation that Tsimberidou et al. teaches a method of treating AMM with TNF-a inhibitors such as Etanercept and Man et al. teaches the instant compound as a TNF-alpha inhibitor. Pages 6-7 of the Office Action. Applicant submits an article evidencing that the Office cannot rely on TNF-alpha activity to support the current rejection. (See Ramanarayanan submitted herewith (Exhibit 1)). The authors reviewed literature of phase I and II studies involving anti-TNF-therapy, and explored the activity and tolerance of TNF-alpha inhibitors in various hematological malignancies including MPD. They reported that Etanercept as a single agent did not yield significant

responses. The authors concluded that anti-TNF-alpha therapy by itself does not induce therapeutic response and that combination therapy with TNF-alpha inhibitors has to be evaluated to determine their role in MPD. Thus, not all TNF-alpha inhibitors treat MPD, and the rejection fails.

Examiner's response:

First, in the Ramanarayanan report there is no specific reference to a study for agnogenic myeloid metaplasia (AMM) which is the disease that Tsimberidou is referring to. The reference by Ramanarayanan simply talks about myeloproliferative diseases (MPD) in general without specifying any particular disease.

Second: contradictory results are very common in science. So the skill in the art, knowing the teachings of Tsimberidou will be motivated to treat AMM with a compound that reduces the amount of free (unbound) TNF-alpha, like Etanercept or Thalidomide as taught by Tsimberidou or like Compound A as taught by Man, despite any contradictory reference.

Applicant argues:

Further, Tsimberidou et. al. teaches away from the claimed invention. Tsimberidou et. al. reports that no responses were seen with Etanercept treatment (pages 237 and 240, second column).

Tsimberidou et al. also states that current treatments other than: allogenic stem cell transplantation, including hydroxyurea, alpha-interferon, androgens, thalidomide, and splenectomy are ultimately ineffective in AMM patients (page 240, 1st column). The

phrase "other than" means that the treatments using compounds cited after the phrase, but nothing else, are effective against AMM. Because the instant compound is not one of the cited compounds after the phrase "other than," Tsimberidou et al. teaches that the instant compound is not effective against AMM. Thus, for purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Peterson, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.) See also In re Geis'ler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (noting that a showing "that the art in any material respect taught away from the claimed invention" can rebut an obviousness allegation) (internal quotation marks omitted); see also M.P.E.P.§ 2141.02(VI) ("A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.").

Examiner's response:

There is nowhere in the Tsimberidou reference a statement that teaches away from the claimed invention or that says that no responses were seen with Etanercept. To the contrary, Tsimberidou states: "We conducted a pilot study to assess the safety of soluble TNF receptor etanercept in patients with refractory hematologic malignancies like AMM" (see page 237, left column). "Three patients with AMM improved (two showed hematologic improvement, and one showed a reduction in liver and spleen size)" (see page 237, left column, last sentence). "Our results are in accordance with those reported by Steensma et. al. ((Blood (2001) 98:628a) who found that Enbrel

(Etanercept) resulted in improvement in erythropoiesis in 3 of 20 patients with AMM (15%), normalization in platelet count in one patient (5%), and reduction in the spleen size of one patient (5%). Notably, in the same study, Enbrel was associated with improvement in constitutional symptoms in 12 patients (60%)" (see page 246, left column, third paragraph).

Regarding the statement by Tsimberidou: "Current treatment options other than allogeneic stem cell transplantation, including hydroxyurea, alpha-interferon, androgens, thalidomide, and splenectomy, are ultimately ineffective in patients with AMM, and novel agents are required", means that up until Tsimberidou's publication: allogeneic stem cell transplantation, including hydroxyurea, alpha-interferon, androgens, thalidomide, and splenectomy, were the only methods known to be effective against AMM, but now Tsimberidou is disclosing a new treatment (i.e. the administration of Etanercept) for AMM that was not known in the past, and as mentioned above is effective in treating AMM. The reason for not being included after the phrase "other than" is because, as mentioned above, Tsimberidou was referring to treatments already known in the literature.

In summary, there is nothing in Tsimberidou's references that teaches against the claimed invention. Applicant suggested that: "Tsimberidou et. al. reports that no responses were seen with Etanercept treatment (pages 237 and 240, second column)". However a careful review of those pages reveals not such statement.

Applicant argues:

In addition, the amendments to the claims render the claims patentable. As amended herein, the instant claims recite, inter alia, a very specific method of treating specific myeloproliferative disease ("MPD," polycythemia rubra vera, primary thrombocythemia, chronic myelogenous leukemia, or agnogenic myeloid metaplasia) that comprises cyclically administering specific amounts (about 5 to 50 mg/day) of a specific compound {2-[(1 S)-I-(3- ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl] -3 -oxo-2,3 -dihydro- 1 H-isoindol-4-yl } - amide (Compound A). In view of the instant amendments, the Office's rejections are now moot. Indeed, the limitations of the instant claims, when considered in combination, render the instant claims non-obvious over the cited art under 35 U.S.C. § 103. The cited art does not provide any reason to pursue the very unique and specific MPD treatment method as claimed. The cited references are devoid of any meaningful predictive value with respect to the claimed method that requires at least: (1) using the specific amounts (5 to 50 mg/day) of the recited compound for treating specific MPD, and (2) by cyclically administering it in particular dosing regimens. These claim elements are not taught or suggested in the cited art. Applicant respectfully points out that the PTO bears the burden of establishing a case of prima facie obviousness against the claims as a whole. That is, all the claim elements must be considered in a 103 rejection. *Abbott Laboratories v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008). Cited art simply fails to do so. Indeed, the Office recognizes that Tsimberidou et al. does not teach the use of the instant compound in the recited amount for treating any MPD. Office Action, page 6.

Man does not cure this deficiency since it is silent as to the use of the recited compound in treating any MPD. The Examiner has provided no specific source of motivation to combine the teachings of the references for the particular claimed cyclic therapy. Therefore, the instant rejection amounts to the mere allegation of a motivation to combine the cited references, simply because some, but not all, of the elements of the instant claims are present individually in the references. This does not meet the legal requirement for a *prima facie* case of obviousness. Abbott, 544 F.3d at 1351; see also *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). In this case, there is no motivation to combine the teachings of the cited art in the claimed method for treating specific MPD using the specific amounts (5 to 50 mg/day) of the recited compound by cyclically administering them in particular dosing regimens.

The Office Action, however, alleges that dose optimization is routine practice in the pharmaceutical art. Office Action, page 7. In this regard, it appears the Office Action takes the position that all dosage regimens are per se obvious. This inflexible approach to an obviousness determination was expressly prohibited in KSR, where the Supreme Court stated that "when a court transforms [a] general principle into a rigid rule that limits the obviousness inquiry...it errs." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). See also MPEP §2144.07 ("Use of per se rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. § 103").

Indeed, courts have held claims reciting dosage limitations to be non-obvious when the prior art provides no basis to pursue the recited dosage. See, e.g., *In re Wiggins*, 397 F.2d 356, 360 (C.C.P.A. 1968) (reversing Board's rejection of composition claim reciting dosage limitation in part because of prior art's "failure to suggest appellant's claimed dosage amounts."); *Ex parte Boden*, 2008 WL 5376662; *Ex parte Eisenhardt*, No. 1999-1229, 2002 WL 1801461 at *4 (Bd. Pat. App. & Interf. 1999) (reversing in part examiner's obviousness rejection of composition claims because dosage limitations were not addressed); *Ex Parte Woldemussie*, No. 95-4823, 1995 WL 1696895 (Bd. Pat. App. & Interf. 1995) (unpublished decision) (reversing examiner's obviousness rejection of claims to method of administering a composition comprising specific doses, stating that "the examiner should determine whether it would have been obvious to one of ordinary skill in the art to adjust the dosage to a value within the claimed range."); *Ex Parte Pickar*, No. 2004-1478, 2004 WL 4983341 at *2 (Bd. Pat. App. & Interf. 2004) (unpublished decision) (reversing in part examiner's obviousness rejection because "the examiner has pointed to nothing in the [cited] reference that suggests the dosage range recited in [the] claim ....").

To say that the development of a dosage or dosage regimen is routine is an oversimplification of drug development and belittles the significance of successfully developing a dosage or dosage regimen. The successfully development of a dosage or dosage regimen is an inventive contribution that is the product of time, effort expense, and ingenuity, which should not be glossed over as a mere "routine" act.

Even if the act of administering a particular dosage or dosage regimen is within the purview of a skilled artisan, there still needs to be reason for that skilled artisan to pursue the particular dosage or dosage regimen in the first place. Indeed, for a determination of obviousness, it is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. KSR, 127 S. Ct. at 1741. In the context of the instant claims, even ifa skilled artisan could routinely perform the claimed dosage regimen, that skilled artisan would not be able to predict, absent teachings to the contrary, whether any particular dosage regimen would actually be effective without the benefit of hindsight. Under KSR, the hallmark of a proper obviousness determination is predictability, which the cited references do not provide.

Examiner's response:

Man teaches that compound A (see page 67, Example 57) belongs to a class of compounds that are non-polypeptide isoindoline derivatives that decrease the levels of TNF-alpha (see page 1, lines 6-7). The compounds can be used under the supervision of a qualified professional, to inhibit undesirable effects of TNF-alpha (see page 22, lines 1-3).

Man further teaches that inhibition of TNF-alpha by these compounds can be conveniently assayed using methods known in the art (see page 20, lines 6-9). It further teaches that dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 1 to about 1,000 mg/day as needed in single or

multiple daily administrations. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF-alpha activity for other TNF-alpha mediated disease states by the compounds of the present invention (see page 22, lines 12-18).

The dosage taught by Man (1 mg to about 1,000 mg/day) of compound A encompasses the instant claim dosage (5 mg to about 50 mg). MPEP 2144.05 states: "In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Even a slight overlap in range establishes a *prima facie* case of obviousness. *In re Peterson*, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003).

Regarding the cyclic administration of compound A, the Examiner refers to Goodman and Gilman's The Pharmacological Basis of Therapeutics (Tenth Edition (2001), McGraw Hill, Chapter I, pages 3-29) cited for evidentiary purposes and as part of the rejection *per se*. Goodman and Gilman's teach that dosage regimen optimization is routine practice in the pharmaceutical art. For example on pages 27 and 28 under the heading: Individualizing dosage, the authors mention that: "A rational dosage regimen is based on knowledge of pharmacokinetic parameters (F, CL, Vss and t1/2) and some information about rates of absorption and distribution of the drug". They also teach: "Individualization of the dosage regimen to a particular patient is, therefore, critical for optimal therapy. The pharmacokinetic principles, described above, provide a

basis for modifying the dosage regimen to obtain a desired degree of efficacy with a minimum of unacceptable adverse effects."

In other words, since the prior art already teaches a dose regimen that overlaps with the current one, and since dose optimization is standard practice in the pharmaceutical art, it would have been prima facie obvious for the skilled in the art to determine the best dosage regime for a particular patient, thus resulting in the practice of the instant invention.

Applicant argues:

Further, Tsimberidou et al. discloses that Etanercept at a dosage of 25 mg weekly was well tolerated (page 240, 2nd column). Thus, Tsimberidou et al. teaches away from the claimed methods using the recited amounts (5 to 50 mg ~ of the instant compound in treating MPD.

Examiner's response:

Etanercept and Compound A are two different compounds with different efficacies, so different dose regimens for these two compounds are expected. As discussed above, Man teaches a dose of Compound A from about 1 to about 1,000 mg/day as needed, which encompasses the instant dose amount of 5 mg to 50 mg per day.

Applicant argues:

Further, assuming that the Patent Office is correct and the use of TNF-a inhibitor in treating MPD is suggested by the cited art, the PTO has not presented evidence to demonstrate that the prior art provides the required reasonable expectation of success. Tsimberidou et al. concludes that no responses were seen with Etanercept treatment (pages 237 and 240, 2na column). More importantly, Applicant submitted a publication showing that anti-TNF-a therapy by itself including Etanercept does not induce therapeutic response in treating MPD (see Ramanarayanan submitted herewith). In view of this teaching, one of ordinary skill in the art would not expect that every compound demonstrating TNF-ct inhibition would be useful in treating MPD. Without more specific guidance in the art, no reasonable expectation exists to use the specific compound of the instant methods for the treatment of MPD. KSR, 127 S.Ct. at 1739 and 1742 (an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results"). Further, the courts have long recognized the unpredictability of the biological properties of chemical compounds. ,See, e.g., *In re Eli Lilly & Co., 902 F.2d. 943, 948* (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties..."). Thus, because the Patent Office has not presented evidence of a reasonable expectation of success, a *prima facie* case of obviousness has not been made.

Examiner's response:

As discussed above, there is nothing in Timberidou's reference that teaches against the instant invention, to the contrary, Tsimberidou teaches a method of treating AMM with the TNF-alpha inhibitor Etanercept (see discussion above). Also,

Tsimberidou refers to a second reference that obtained similar results (Steensma et. al. ((Blood (2001) 98:628a)) (see also above discussion). In summary, there is enough guidance in Tsimberidou's reference for the skilled in the art to further try other TNF-alpha inhibitors for the treatment of AMM.

Conclusion

No claims are allowed.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
May 28, 2010.

/Frederick Krass/
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